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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/126,816	07/31/98	VON EICHEL-STREIBER C	PM254992

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EXAMINER	
BURKE, J	
ART UNIT	**PAPER NUMBER**
1642	13

DATE MAILED: 09/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/126,816	Von Eichel-Streiber et al
Examiner	**Group Art Unit**
Julie E. Burke (Reeves), Ph.D.	1642

☒ Responsive to communication(s) filed on *5 Jul 2000*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-6 and 11-20* is/are pending in the application.

Of the above, claim(s) *1-6 and 11* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *12-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1-6 and 11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected Inventions. Election was made **without** traverse in Paper No. 8.

2. Claims 1-6 and 11-20 are pending. Claims 7-10 have been canceled. Claims 12-20 have been added and are under examination.

3. The text of those sections of Title 35, U.S.C. Code not included in this Office Action can be found in a prior Office Action.

4. The following Office Action contains some NEW GROUNDS of rejection that have been necessitated by amendment.

Compliance with the Sequence Requirements

5. This application is now incompliance with the Requirements For Patent Applications Containing Nucleotide And/or Amino Acid Sequence Disclosures.

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The Title recites a method while the claims recite products.

7. The disclosure stands objected to because of the following informalities:

a. the priority claimed for PCT/EP97/000426 is not recited in the first line of the specification.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

8. Newly added Claims 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Newly added claims 12-20 are indefinite for reciting amino acid numbers "the first 1020 amino acids" and "amino acids 1021-1700" because a sequence of Clostridium sordellii lethal toxin has not been provided from which to identify the numbered fragments. The claims recite from the amino terminus, however, a protein may possess several "amino termini" depending upon degree of posttranslational processing it obtains. For examples, the amino terminal methionine residue is often clipped off; many secreted proteins contains signal sequences which are removed upon translocation across the membrane; and enzyme often exist in pre- and pro-states. Post translational processing creates a variety of proteins which do not have a common amino termini. Absent a sequence in the claims, the boundaries of the peptide fragments recited in the claims are vague and indefinite. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

b. Newly added Claims 13-15, 17 and 19 are indefinite for reciting an "immunotoxin" as the only portion recited in the claims is a toxin. No antibody or other "immunological molecule is recited int the claims. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

9. Newly added Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunotoxin fusion protein comprising an antibody or antigen binding fragment thereof, a translocation domain capable of translocating the LT catalytic domain across the cytoplasmic membrane of a cell and the Clostridium sordellii Lethal toxin (LT) catalytic domain having glucosyltransferase activity, composition comprising such, a method of manufacturing compositions comprising the immunotoxin and a therapeutically acceptable adjuvant or carrier, does not reasonably provide enablement for compositions comprising any target cell specific binding domain, or any polypeptide with the toxic activity of the catalytic domain of the toxin LT from Clostridium sordellii LT, manufacturing a therapeutic composition, or of a composition for treating a pathological condition in a patient involving activation of at least one Ras proto-oncoprotein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons set forth in the previous Office Action, as evidenced by .

a. The claim broadly recite any composition for treating any pathological condition characterized by activation of Ras onco-proteins, wherein the composition comprises any target cell specific binding domain, including an active fragment of an antibody, a translocation domain and a polypeptide with the toxic activity of the catalytic domain of toxin LT from Clostridium

sordellii LT. The claims also broadly recite a method of manufacturing a therapeutic agent by combining a therapeutically useful amount of an immunotoxin with a carrier or adjuvant.

b. The claims now recite particular amino acid sequence numbers. In view of the post translation processing, one skilled in the art would not be able to make the claimed fragments which would have the requisite activity, without undue experimentation. In view of the various allelic versions and modified versions of the LT, one skilled in the art would not know which sequence to begin counting from. Merely stating that the numbering begins at the amino acid terminal, is not sufficient to overcome this rejection, in view of the various post translationally modified sequences. For examples, the amino terminal methionine residue is often clipped off; many secreted proteins contains signal sequences which are removed upon translocation across the membrane; and enzyme often exist in pre- and pro-states. Post translational processing creates a variety of proteins which do not have a common amino termini. Absent a sequence in the claims, undue experimentation would be required by one skilled in the art to determine which boundaries of the peptide fragments recited in the claims have the required activity. It appears as though the amino acid sequence of LT is an essential feature of the claimed invention, however this sequence has not been incorporated by reference into the specification. Demonstrating that there exists only one art-recognized Clostridium sordellii lethal Toxin, which has only one sequence and is produced in only one post translationally modified form and properly incorporating that sequence by reference into the specification would be sufficient to obviate this rejection.

c. The newly added claims 13-15, 17 and 19 recite an immunotoxin, however no antibody or antigen binding fragment is specified in the claims. The claims broadly read upon linking the LT fragment to any "immune" molecule, such as a T cell receptor subunit, a immunoglobulin hinge region or antibody constant region. One skilled in the art would not be able to make an "immunotoxin" using an antibody hinge region, for example, because such an immunotoxin would not bind the target cell without undue experimentation. As evidenced by Rudikoff, Amit and Panka, in the previous Office Action, antigen binding requires antibody variable region sequences, including framework regions and complementarity determining regions, which are lacking in the broad claims. Amending the claims to recite an immunotoxin which comprising an antibody or an antigen binding fragment thereof in addition to the toxin component would be sufficient to obviate this portion of the rejection.

d. Newly added claims 17-20 recite "manufacturing a therapeutic composition" or "composition for treating a pathological condition in a patient involving activation of at least one Ras proto-oncoprotein". The specification does not support the use of broadly claimed immunotoxins for the broad scope for all the possible therapies and treatments of any pathological condition in a patient involving activation of at least one Ras proto-oncoprotein. See In re Frederiksen & Nielsen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). Amending the claims to delete the phrase "therapeutic" and to delete the phrase "for treating a pathological condition in a patient involving activation of at least one Ras proto-oncoprotein" would obviate this portion of the rejection.

Priority

10. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under domestic or foreign priority as follows: copies of the PCT and the EPO parent documents are not present in the file. Therefore, the Examiner is unable to determine whether the instant claims are to be granted priority back to the dates claimed. Absent the priority documents, the claims are given the priority date of 7/31/98 of the instant application.

Claim Rejections - 35 U.S.C. § 102

11. Newly added Claims 12-15, 17, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by any of Popoff (Infection and Immunity Vol 55(1)35-43 1987) or Roberts et al (WO/9422476 published 13 Oct 1994), as evidenced by Chaves-Olarte et al (J Biol Chem Vol 274 No 16 11046-11052 4/99), for the reasons set forth in the previous Office Action and the new grounds of rejection necessitated by amendment.

a. Claim 12-15, 17, 19 recite a peptide fragment of Clostridium sordellii LT consisting essentially of the first 1020 amino acids from the N-terminal; an immunotoxin comprising such; compositions comprising such and a method of manufacturing compositions comprising such. Applicant is reminded that the intended use of a product claim carries no patentable weight [MPEP 2111.02], therefore, the intended phrases in claim 19 are not given patentable weight for this rejection. It is noted that the term "immunotoxin" in claims 13-15, 17 and 19 is given no patentable weight because the claims do not recite which part, if any, of the

composition has anything to with the immune system. "Consisting essentially of" does not mean "consisting of" Ex parte Appeldorn & Gilkeson (PQ BdApp 159 USPQ 791). Applicant's use of the open-ended term "comprising" in claims 13-14, for examples, fails to exclude unrecited steps and leaves claims open for inclusion of unspecified ingredients, even in large amounts. See In re Horvitz, 168 F 2d 522, 78 USPQ 79 (CCPA 1948) and Ex parte Davis et al, 80 USPQ 448 (PTO d. App. 1948). The boundaries of the amino acid fragments recited in claims 12. 14. 15 are impossible to determine absent the disclosure of a LT amino acid sequence.

b. Popoff teach a homogenous LT preparation characterized as a single band on silver stained SDS polyacrylamide gels (page 42, col 1, fifth full paragraph). Popoff teach that the purified LT was lethal for mice (page 40, first full paragraph). Popoff teach a composition comprising the purified LT in the therapeutically acceptable carrier or adjuvant PBS (page 36, col 1, fifth full paragraph). Popoff et al teaches the composition which would have the inherent functional property of glycosylating activity.

c. Roberts et al teach vaccines comprising toxoids derived from Clostridium sordellii and a saponin adjuvant (page 2, lines 28-33). Roberts et al's Clostridium sordellii composition would inherently comprise the LT toxin. Robert et al teaches the composition which would have the inherent functional property of glycosylating activity.

d. As evidenced by Chaves-Olarte et al, either of Roberts et al's or Popoff 's lethal toxins of Clostridium sordellii (LT or also known as TcsL, see page 11046, abbreviations and bridging paragraph cols 1-2) contain a catalytic domain (a polypeptide with the toxic activity of

the catalytic domain of toxin LT from Clostridium sordellii LT), a hydrophobic domain (translocation domain) and a receptor binding domain (the target cell specific binding domain) as shown in the Schematic representation of TcsL-1552. Fig 1). Chaves-Olarte is noted as evidence to show that the proteins of either Popoff et al or Roberts et al re the same as those claimed and would inherently have the properties ascribed by the claims. Thus the limitations of the claims have been met.

e. The response set forth on page 6 has been considered carefully but is deemed not to be persuasive. The response argues that Popoff does not disclose any DNA sequence, however the claims do not require any DNA sequence. The response argues that the sequence was not known a the time by Popoff, however, the sequence is not present in this application or these claims either.

f. The response argues that the disclosure of Roberts does not suggest a combination with Popoff. Is it noted that the instant rejection has been set forth, in the alterative, under 35 U.S.C. 102(b) and is not an obvious-type rejections et forth under 35 U.S.C. 103.

g. The response correctly states that Chaves-Olarte has a publication date after the priority date. Chaves-Olarte is a recent publication used to evidence that the compositions of the prior art Popoff et al or Roberts et al read upon the claimed invention.

12. Newly added Claim 12-15, 17, 19 are rejected under 35 U.S.C. 102(a or b) as being anticipated by any of Green et al (Gene 161:57-61 1995) or von Eichel-Streiber et al (Mol

Microbiol Vol 17(2) 313-321 1995) as evidenced by Chaves-Olarte et al (J Biol Chem Vol 274 No 16 11046-11052 4/99), for the reasons set forth in the previous Office Action and reasons set forth in the previous 102 rejection and set forth below..

a. The claims and their interpretation have been described above. The evidence provided by Chaves-Olarte et al has been described above.

b. In view of the fact that the priority documents are missing and in view of the fac the exact date of publication for the Green et al and von Eichel-Streiber references were not available at the time this Office Action was produced, the rejection is made under both 35 U.S.C. 102(a) and 35 U.S.C. 102(b). Once the priority date and reference publication dates are available, the rejection will be amended accordingly.

c. Green et al teach cloning and characterization of the cytotoxic L-encoding gene of Clostridium sordellii. The open reading frame shows a highly conserved hydrophobic domain (translocation domain) and a highly conserved carboxyl terminal.

d. Von Eichel-Streiber et al teach that the immunologically, ToxA and ToxB of C dificils are related to lethal toxin of Clostridium sordellii (page 313, col 2, second full paragraph). Von Eichel-Streiber et al teach that "morphological changes induced by the ToxB-1470 protein and LT of C. Sordellii were indistinguishable"(page 317, col 1, last paragraph; Fig 4) and that the cytopathic effects of ToxB-1470 are indistinguishable from those caused by the lethal toxin of Clostridium sordellii (see Abstract). Von Eichel-Streiber teaches that the toxins of C. Difficile contain a amino terminal toxic domain, an intermediary translocation domain and a final C

terminal region contributing to cellular binding and that this organization resembles that of other bacterial toxins including all clostridium neurotoxins (page 319, final paragraph).

e. The response set forth on page 6-7 has been considered carefully but is deemed not to be persuasive. The response argues that although Green teaches the C. Sordellii LT DNA sequence, "no mode of action" is present and "nor is the glucosylation of Ras mentioned or predicted". The fact remains that the claims recite products and not method of using the products. The intended use recited in the chains is not given any patentable weight for this rejection. The claims do not mention "glucosylation of Ras" limitation argued. The mode of action is not relevant for a product claim. The claims recite fragment which comprise the first 1020 amino acids of LT. "Comprising" is open language which reads upon any protein which contains that fragment, ie the full length protein. Even if the claims were limited to consisting of amino acids 1-1020, absent a sequence from which to count out this fragment the metes and bounds of the claims are impossible to determine. For the purposes of compact prosecution the claims are interpreted as broadly as possible.

Claim Rejections - 35 U.S.C. § 103

13. Claims 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Popoff (supra) or von Eichel-Streiber et al (supra) in combination with Blakey et al (Antibody Toxin Conjugates: A Perspective. Waldmann H. (ed): Monoclonal Antibody Therapy. Prog. Allergy. Basel, Karger, 1988 vol. 45 pp 50-90), for the reasons set forth in the previous Office Action and for the reasons set forth above.

a. Claim 13, 14, 15, 17, 19 and their interpretation have been described above. Claims 16, 18 and 20 recites an immunotoxin comprising the various LT fragments and an antibody or an active fragment thereof.

b. Both of Popoff or von Eichel-Streiber et al have been discussed above, individually, with regards to the Clostridium sordellii LT toxin. However, none of Popoff (supra) or von Eichel-Streiber et al provide the methods to conjugate the toxin to an antibody to create the claimed immunotoxin.

c. Blakey et al describe the rationale and methods for coupling antibodies to toxins for pharmaceutical therapy. In particular, Blakey et al disclose conjugating bacterial toxins (see Figs 2 and 3) to antibodies specific for tumour associated antigens.

d. It would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to have chemically conjugated any of the prior art's Clostridium sordellii LT to antibodies or active fragments thereof directed against tumour associated antigens (TAA), as described by Blakey et al. Further, one skilled in the art would have been motivated to add a toxin to the anti-TAA antibody for the express purpose of creating a anti-TAA immunotoxin and, given the rationale provided by Blakey et al, one would have had a reasonable expectation of success in coupling a toxin to an antibody. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The chemical linkages produced by Blakey et al's methods would comprise covalent bonds as required by the claims. Therefore the

invention, as a whole, was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

e. The response set forth on page 8-9 has been considered carefully but is deemed not to be persuasive. The response argues that the primary references have been distinguished. This is not persuasive because the previous 102 rejections have been maintained for the reasons set forth above.

14. Claims 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al in combination with either of Vitetta et al (Science Vol 238:1038 11/87) or Sandhu (Critical reviews in Biotechnology Vol 12(5/6) 437-462 1992)

a. Claims and their interpretation have been described above.

b. Green et al has been discussed above with regards to the Clostridium sordellii LT toxin and the C. Dificille cytotoxin B. Green et al fails to provide the methods to make a fusion protein comprising the LT or ToxB toxin and an antibody to cell specific binding domain to create the claimed immunotoxin. However this deficiency is made up for by the teachings of either of Vitetta et al or Sandhu et al.

c. Vitetta et al teach that the development of third generation IT [immunotoxins] as produced by recombinant DNA technology would be advantageous to prepare homogenous IT's (page 1103, cols 1-2, bridging paragraph). Vitetta et al teach in general that the DNA encoding the toxin region could be fused to DNA encoding the antigen combining region of an antibody.

Vitetta et al teach that antibodies may be directed against determinants on neoplastic cells (pages 1098-9 bridging paragraph). Vitetta et al teach that by cloning genes for relevant toxins and antibodies and manipulating these genes, nature's molecules can be redesigned in a more rational manner.

d. Sandhu teach that bacterial toxins have been used in developing targeting toxins for the treatment of cancer (page 455, first full paragraph). Sandhu teach using recombinant DNA technology to synthesize antibody/toxin fusion proteins in E. coli. Sandhu teach that these fusion proteins selectively kill cells bearing the appropriate antigens and provide motivation for making immunotoxins for the treatment of cancer (page 455, col 2 second full paragraph).

e. It would have been prima facie obvious for one of ordinary skill in the art at the time the claimed invention was made to have used recombinant DNA technology to ligate DNA encoding any of the Green et al's Clostridium sordellii LT to DNA encoding antibodies or active fragments thereof directed against tumour associated antigens (TAA), as described by either of Vitetta et al or Sandhu. Further, one skilled in the art would have been motivated to add a toxin to the anti-TAA antibody for the express purpose of creating a anti-TAA immunotoxin and, given the rationale provided by either of Vitetta et al or Sandhu, one would have had a reasonable expectation of success in using recombinant DNA technology to couple a toxin to an antibody. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The peptide linkages produced by either of either of Vitetta et al or Sandhu's methods would comprise

covalent bonds as required by the claims. Therefore the invention, as a whole, was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

f. The response set forth on page 8-9 has been considered carefully but is deemed not to be persuasive. The response argues that the primary references have been distinguished. This is not persuasive because the previous 102 rejections have been maintained for the reasons set forth above.

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Burke, née Reeves, Ph.D, whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

JBurke

Julie E. Burke, née Reeves, Ph.D.

Primary Patent Examiner

(703) 308-7553

JULIE BURKE
PRIMARY EXAMINER